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64-Slice Computed Tomographic Angiography for the Diagnosis of Intermediate Risk Coronary Artery Disease

An Evidence-Based Analysis

Presented to the Ontario Health Technology Advisory Committee in January, 2010

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

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Table of Contents

List of Tables & Figures

List of Abbreviations

AUC	Area under the curve
CAD	Coronary artery disease
CI	Confidence interval(s)
CT	Computed tomography
CTA	Computed tomographic angiography
DOR	Diagnostic odds ratio
MAS	Medical Advisory Secretariat
NPV	Negative predictive value
NS	Not significant
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
PPV	Positive predictive value
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SE	Standard error
SROC	Summary receiver operating characteristic

Executive Summary

In July 2009, the Medical Advisory Secretariat (MAS) began work on Non-Invasive Cardiac Imaging Technologies for the Diagnosis of Coronary Artery Disease (CAD), an evidence-based review of the literature surrounding different cardiac imaging modalities to ensure that appropriate technologies are accessed by patients suspected of having CAD. This project came about when the Health Services Branch at the Ministry of Health and Long-Term Care asked MAS to provide an evidentiary platform on effectiveness and cost-effectiveness of non-invasive cardiac imaging modalities.

After an initial review of the strategy and consultation with experts, MAS identified five key non-invasive cardiac imaging technologies for the diagnosis of CAD. Evidence-based analyses have been prepared for each of these five imaging modalities: cardiac magnetic resonance imaging, single photon emission computed tomography, 64-slice computed tomographic angiography, stress echocardiography, and stress echocardiography with contrast. For each technology, an economic analysis was also completed (where appropriate). A summary decision analytic model was then developed to encapsulate the data from each of these reports (available on the OHTAC and MAS website).

The Non-Invasive Cardiac Imaging Technologies for the Diagnosis of Coronary Artery Disease series is made up of the following reports, which can be publicly accessed at the MAS website at: www.health.gov.on.ca/mas or at www.health.gov.on.ca/english/providers/program/mas/mas_about.html

1. Single Photon Emission Computed Tomography for the Diagnosis of Coronary Artery Disease: An Evidence-Based Analysis
2. Stress Echocardiography for the Diagnosis of Coronary Artery Disease: An Evidence-Based Analysis
3. Stress Echocardiography with Contrast for the Diagnosis of Coronary Artery Disease: An Evidence-Based Analysis
4. 64-Slice Computed Tomographic Angiography for the Diagnosis of Coronary Artery Disease: An Evidence-Based Analysis
5. Cardiac Magnetic Resonance Imaging for the Diagnosis of Coronary Artery Disease: An Evidence-Based Analysis

Pease note that two related evidence-based analyses of non-invasive cardiac imaging technologies for the assessment of myocardial viability are also available on the MAS website:

1. Positron Emission Tomography for the Assessment of Myocardial Viability: An Evidence-Based Analysis
2. Magnetic Resonance Imaging for the Assessment of Myocardial Viability: an Evidence-Based Analysis

The Toronto Health Economics and Technology Assessment Collaborative has also produced an associated economic report entitled:

The Relative Cost-effectiveness of Five Non-invasive Cardiac Imaging Technologies for Diagnosing Coronary Artery Disease in Ontario [Internet]. Available from: http://theta.utoronto.ca/reports/?id=7

Objective

The objective of this report is to determine the accuracy of computed tomographic angiography (CTA) compared to the more invasive option of coronary angiography (CA) in the detection of coronary artery disease (CAD) in stable (non-emergent) symptomatic patients.

CT Angiography

CTA is a cardiac imaging test that assesses the presence or absence, as well as the extent, of coronary artery stenosis for the diagnosis of CAD. As such, it is a test of cardiac structure and anatomy, in contrast to the other cardiac imaging modalities that assess cardiac function. It is, however, unclear as to whether cardiac structural features alone, in the absence cardiac function information, are sufficient to determine the presence or absence of intermediate pre-test risk of CAD.

CTA technology is changing rapidly with increasing scan speeds and anticipated reductions in radiation exposure. Initial scanners based on 4, 8, 16, 32, and 64 slice machines have been available since the end

of 2004. Although 320-slice machines are now available, these are not widely diffused and the existing published evidence is specific to 64-slice scanners. In general, CTA allows for 3-dimensional (3D) viewing of the coronary arteries derived from software algorithms of 2-dimensional (2D) images.

The advantage of CTA over CA, the gold standard for the diagnosis of CAD, is that it is relatively less invasive and may serve as a test in determining which patients are best suited for a CA. CA requires insertion of a catheter through an artery in the arm or leg up to the area being studied, yet both tests involve contrast agents and radiation exposure. Therefore, the identification of patients for whom CTA or CA is more appropriate may help to avoid more invasive tests, treatment delays, and unnecessary radiation exposure. The main advantage of CA, however, is that treatment can be administered in the same session as the test procedure and as such, it's recommended for patients with a pre-test probability of CAD of ≥80%. The progression to the more invasive CA allows for the diagnosis and treatment in one session without the added radiation exposure from a previous CTA.

The visibility of arteries in CTA images is best in populations with a disease prevalence, or pre-test probabilities of CAD, of 40% to 80%, beyond which patients are considered at high pre-test probability. Visibility decreases with increasing prevalence as arteries become increasingly calcified (coronary artery calcification is based on the Agaston score). Such higher risk patients are not candidates for the less invasive diagnostic procedures and should proceed directly to CA, where treatment can be administered in conjunction with the test itself, while bypassing the radiation exposure from CTA.

CTA requires the addition of an ionated contrast, which can be administered only in patients with sufficient renal function (creatinine levels >30 micromoles/litre) to allow for the clearing of the contrast from the body. In some cases, the contrast is administered in patients with creatinine levels less than 30 micromoles/litre.

A second important criterion for the administration of the CTA is patient heart rate, which should be less than 65 beats/min for the single source CTA machines and less than 80 beats/min for the dual source machines. To decrease heart rates to these levels, beta-blockers are often required. Although the accuracy of these two machines does not differ, the dual source machines can be utilized in a higher proportion of patients than the single source machines for patients with heart beats of up to 80 beats/min. Approximately 10% of patients are considered ineligible for CTA because of this inability to decrease heart rates to the required levels. Additional contra-indications include renal insufficiency as described above and atrial fibrillation, with approximately 10% of intermediate risk patients ineligible for CTA due these contraindications. The duration of the procedure may be between 1 and 1.5 hours, with about 15 minutes for the CTA and the remaining time for the preparation of the patient.

CTA is licensed by Health Canada as a Class III device. Currently, two companies have licenses for 64-slice CT scanners, Toshiba Medical Systems Corporation (License 67604) and Philips Medical Systems (License 67599 and 73260).

Research Questions

1. How does the accuracy of CTA compare to the more invasive CA in the diagnosis of CAD in symptomatic patients at intermediate risk of the disease?
2. How does the accuracy for CTA compare to other modalities in the detection of CAD?

Research Methods

Literature Search

A literature search was performed on July 20, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2004 until July 20, 2009. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any relevant studies not identified through the search. The quality of evidence was assessed as high, moderate, low or very low according to GRADE methodology.

Inclusion Criteria

- English language articles and English or French-language HTAs published from January 1, 2004 to July 20, 2009.
- Randomized controlled trials (RCTs), non-randomized clinical trials, systematic reviews and meta-analyses.
- Studies of symptomatic patients at intermediate pre-test probability of CAD.
- Studies of single source CTA compared to CA for the diagnosis of CAD.
- Studies in which sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) could be established. HTAs, SRs, clinical trials, observational studies.

Exclusion Criteria

- Non-English studies.
- Pediatric populations.
- Studies of patients at low or high pre-test probability of CAD.
- Studies of unstable patients, e.g., emergency room visits, or a prior diagnosis of CAD.
- Studies in patients with non-ischemic heart disease.
- Studies in which outcomes were not specific to those of interest in this report.
- Studies in which CTA was not compared to CA in a stable population.

Outcomes of Interest)

- CAD defined as ≥50% stenosis.

Comparator

- Coronary angiography.

Measures of Interest

- Sensitivity, specificity;
- Negative predictive value (NPV), positive predictive value (PPV);
- Area under the curve (AUC) and diagnostic odds ratios (DOR).

Results of Literature Search and Evidence-Based Analysis

The literature search yielded two HTAs, the first published by MAS in April 2005, the other from the Belgian Health Care Knowledge Centre published in 2008, as well as three recent non-randomized clinical studies. The three most significant studies concerning the accuracy of CTA versus CA are the CORE-64 study, the ACCURACY trial, and a prospective, multicenter, multivendor study conducted in the Netherlands. Five additional non-randomized studies were extracted from the Belgian Health Technology Assessment (2008).

To provide summary estimates of sensitivity, specificity, area under the SROC curve (AUC) and diagnostic odds rations (DORs), a meta-analysis of the above-mentioned studies was conducted. Pooled

estimates of sensitivity and specificity were 97.7% (95%CI: 95.5% - 99.9%) and 78.8% (95%CI: 70.8% - 86.8%), respectively. These results indicate that the sensitivity of CTA is almost as good as CA, while its specificity is poorer. The diagnostic odds ratio (DOR) was estimated at 157.0 (95%CI: 11.2 - 302.7) and the AUC was found to be 0.94; however, the inability to provide confidence estimates for this estimate decreased its utility as an adequate outcome measure in this review.

This meta-analysis was limited by the significant heterogeneity between studies for both the pooled sensitivity and specificity (heterogeneity Chi-square p=0.000). To minimize these statistical concerns, the analysis was restricted to studies of intermediate risk patients with no previous history of cardiac events. Nevertheless, the underlying prevalence of CAD ranged from 24.8% to 78% between studies, indicating that there was still some variability in the pre-test probabilities of disease within this stable population. The variation in the prevalence of CAD, accompanied with differences in the proportion of calcification, likely affected the specificity directly and the sensitivity indirectly across studies.

In February 2010, the results of the Ontario Multi-detector Computed Tomography Coronary Angiography Study (OMCAS) became available and were thus included in a second meta-analysis of the above studies. The OMCAS was a non-randomized double-blind study conducted in 3 centers in Ontario that was conducted as a result of a MAS review from 2005 requesting an evaluation of the accuracy of 64-slice CTA for CAD detection. Within 10 days of their scheduled CA, all patients received an additional evaluation with CTA. Included in the meta-analysis with the above-mentioned studies are 117 symptomatic patients with intermediate probability of CAD (10% - 90% probability), resulting in a pooled sensitivity of 96.1% (95%CI: 94.0%-98.3%) and pooled specificity of 81.5% (95%CI: 73.0% - 89.9%).

Summary of Findings

1. CTA is almost as good as CA in detecting true positives but poorer in the rate of false positives. The main value of CTA may be in ruling out significant CAD.
2. Increased prevalence of CAD decreases study specificity, whereas specificity is increased in the presence of increased arterial calcification even in lower prevalence studies.
3. Positive CT angiograms may require additional tests such as stress tests or the more invasive CA, partly to identify false positives.
4. Radiation exposure is an important safety concern that needs to be considered, particularly the cumulative exposures from repeat CTAs.

Background

In July 2009, the Medical Advisory Secretariat (MAS) began work on Non-Invasive Cardiac Imaging Technologies for the Diagnosis of Coronary Artery Disease (CAD), an evidence-based review of the literature surrounding different cardiac imaging modalities to ensure that appropriate technologies are accessed by patients suspected of having CAD. This project came about when the Health Services Branch at the Ministry of Health and Long-Term Care asked MAS to provide an evidentiary platform on effectiveness and cost-effectiveness of non-invasive cardiac imaging modalities.

After an initial review of the strategy and consultation with experts, MAS identified five key non-invasive cardiac imaging technologies for the diagnosis of CAD. Evidence-based analyses have been prepared for each of these five imaging modalities: cardiac magnetic resonance imaging, single photon emission computed tomography, 64-slice computed tomographic angiography, stress echocardiography, and stress echocardiography with contrast. For each technology, an economic analysis was also completed (where appropriate). A summary decision analytic model was then developed to encapsulate the data from each of these reports (available on the OHTAC and MAS website).

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Objective of Analysis

The objective of this report is to determine the accuracy of 64-slice computed tomographic angiography (CTA) compared to the more invasive option of coronary angiography (CA) in the diagnosis of coronary artery disease (CAD) in stable (non-emergent) symptomatic patients.

Ontario Context

The 2005 MAS review indicated that there were approximately 50 64-slice CT scanners in operation worldwide. With respect to the number of machines available in Ontario, the more recent 64-slice machines as well as earlier CT scanners included, Ontario had the lowest number of CT scanners per million population (8 per million) among Canadian provinces (with an average of 11 per million). Despite this, the five-week wait time was similar to the Canadian average of six weeks. With respect to treatments, the Cardiac Care Network reported that 25% of urgent cases, 53% of semi-urgent cases and 21% of elective cases were not receiving cardiac catheterization within the recommended wait times, with potential increased wait times with referrals from CTA. (1) In 2005, 27 Ontario hospitals were expected

to receive 64-slice CT scanners following funding from the Diagnostic and Medical Equipment Fund. In a 2006 Canadian Institute for Health Information (CIHI) report (2), findings of medical technology surveys conducted annually by the Canadian Coordinating Office for Health Technology Assessment from 2003 to 2006, the number of CT scanners had reportedly increased by 180 (or 91%) from 1990 to 2006 in Canada, though it is unclear what proportion were 64-slice machines or higher. In Ontario, 118 scanners were available as of January 1, 2006, or 9.4 scanners per million population; this rate remains lower than the national average of 11.6 scanners per million population. Further, the number of CT scans conducted in Ontario in 2005 was 92 per 1,000 population, also lower than the Canadian average of 98 per 1,000 persons.

CT Angiography

CTA is a cardiac imaging test that assesses the presence and absence, as well as the extent of coronary artery stenosis in the diagnosis of CAD. As such, it is a test of cardiac structure and anatomy, in comparison to the other cardiac imaging modalities, which assess cardiac function. The technology allows for a 3-dimensional viewing of the coronary arteries derived from software algorithms of 2-dimensional images. It is unclear whether cardiac structural features alone, however, in the absence of information on cardiac function, are sufficient to determine the presence or absence of intermediate pre-test risk of CAD.

The advantage of CTA over CA, the gold standard for the diagnosis of CAD, is that it is relatively less invasive and may serve as a test in determining which patients are best suited for a CA. CA requires insertion of a catheter through an artery in the arm or leg up to the area being studied, yet both tests involve contrast agents and radiation exposure. Therefore, the identification of patients for whom CTA or CA is more appropriate is may help to avoid more invasive tests, delays in treatment, and unnecessary radiation exposure form CTA. The main advantage of CA, however, is that treatment can be administered in the same session as the test procedure and as such, it's recommended for patients with a pre-test probability of CAD of ≥80%. The progression to the more invasive CA allows for the diagnosis and treatment in one session without the added radiation exposure from a previous CTA.

CTA technology is changing rapidly with increasing scan speeds and anticipated reductions in radiation exposure. Scanners based on 4, 8, 16, 32, and 64 slice machines have been available since the end of 2004; although 320-slice machines are now available, these are not widely diffused and the existing published evidence is specific to 64-slice scanners.

The visibility of arteries in CTA images is best in populations with disease prevalence, or pre-test probabilities of CAD, of 40% to 80%, beyond which patients are considered at high pre-test probability (Expert consultation, December 2009). Visibility decreases with increasing prevalence as the arteries become increasingly calcified (coronary artery calcification is based on the Agaston score).

Such higher risk patients are not candidates for the less invasive diagnostic procedures and should proceed to CA, where treatment can be administered in conjunction with the test itself, while bypassing the radiation exposure from CTA.

CTA requires the addition of an ionated contrast, which can be administered only in patients with sufficient renal function (creatinine levels >30 micromoles/litre) to allow for the clearing of the contrast from the body. In some cases, the contrast is administered in patients with creatinine levels of less than 30 micromoles/litre. (Expert consultation, December 2009)

A second important criterion for the administration of the CTA is patient heart rate, which should be less than 65 beats/min for the single source CTA machines and less than 80 beats/min for the dual source machines. To decrease heart rates to these levels, beta-blockers are often required. Although the

accuracy of these two machines does not differ, the dual source machines can be utilized in a higher proportion of patients than the single source machines for patients with heart beats up to 80 beats/min. (Expert consultation, November/ December 2009) Approximately 10% of patients are considered ineligible for CTA because of this inability to decrease heart rates to the required levels. Additional contra-indications include renal insufficiency as described above and atrial fibrillation, with approximately 10% of intermediate risk patients being ineligible for CTA due these contraindications. The duration of the procedure may be between 1 and 1.5 hours, with about 15 minutes for the CTA and the remaining time for the preparation of the patient.

CTA is licensed by Health Canada as a Class III device. Currently, two companies have licenses for 64-slice CT scanners, Toshiba Medical Systems Corporation (License 67604) and Philips Medical Systems (License 67599 and 73260).

Evidence-Based Analysis

Research Questions

1. How does the accuracy of CTA compare to the more invasive CA in the diagnosis of CAD in symptomatic patients at intermediate risk of the disease?
2. How does this accuracy for CTA compare to other modalities in the detection of CAD?

Methods

A literature search was performed on July 20, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2004 to July 20, 2009. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any relevant studies not identified through the search.

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- Studies of symptomatic patients at intermediate pre-test probability of CAD.
- Studies of single source CTA compared to CA for the diagnosis of CAD.
- Studies in which sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) could be established. HTAs, SRs, clinical trials, observational studies.

Exclusion Criteria

- Non-English studies.
- Pediatric populations.
- Studies of patients at low or high pre-test probability of CAD.
- Studies of unstable patients, e.g., emergency room visits, or a prior diagnosis of CAD.
- Studies in patients with non-ischemic heart disease.
- Studies in which outcomes were not specific to those of interest in this report.
- Studies in which CTA was not compared with CA in a stable population.

Outcomes of Interest

- CAD defined as ≥50% stenosis in any one artery.

Comparator

- Coronary angiography (CA).

Measures of Interest

- Sensitivity, specificity;
- Negative predictive value (NPV), positive predictive value (PPV);
- Area under the curve (AUC);
- Diagnostic odds ratio (DOR).

Statistical Analysis

Pooled estimates of sensitivity, specificity, and DORs were calculated using a bivariate, binomial generalized linear mixed model. (3) Statistical significance was defined by P values of less than 0.05, where "false discovery rate" adjustments were made for multiple hypothesis testing. (4) The bivariate regression analyses were performed using SAS version 9.2 (SAS Institute Inc.; Cary, NC, USA). Using the bivariate model parameters, summary receiver operating characteristic (sROC) curves were produced using Review Manager 5.0.22 (The Nordiac Cochrane Centre, The Cochrane Collaboration, 2008). The area under the sROC curve was estimated by numerical integration with a cubic spline (default option) using STATA version 10.1 (StataCorp; Texas, USA).

Results of Literature Review and Evidence-Based Analysis

A total of 486 references were identified for review. Included in this EBA were two HTAs, the first published by MAS in April 2005 (1), the other from the Belgian Health Care Knowledge Centre and published in 2008 (5), as well as three most recent non-randomized clinical studies.

Table 1: Summary and Focus of Previous Health Technology Assessments on CTA

Year	Author	Focus of Assessment
2005	Medical Advisory Secretariat (MAS) (1)	To assess the safety, effectiveness and cost-effectiveness of multi-slice CTA compared with CA in the diagnosis and management of people with CAD. *
2008	UK NIHR HTA Programme (6)	To assess the clinical and cost-effectiveness of 64-slice or higher CTA, instead of CA, for diagnosing suspected CAD and assessing people with known CAD.
2008	Belgian Health Care Knowledge Centre (5)	To summarize current evidence on CTA as an imaging modality for native coronary arteries.

* CTA: computed tomographic angiography; CA: coronary angiography; CAD: coronary artery disease.

The MAS HTA reviewed the existing evidence on multi-slice CTA from 2003 to January 2005. (1) The intent of the review was to assess the safety, effectiveness and cost-effectiveness of 16-slice and 64-slice CTA compared with CA in the diagnosis of CAD. At the time, CAD was a relatively new indication for CTA, with 64-slice machines having been made available only in late 2004. Therefore, the 2005 report focuses primarily on 16-slice CTA, a technology that pre-dates the 64-slice machines at the center of the present analysis.

Recommendations from the MAS 2005 review (1) included a field evaluation and a radiation risk review. The Ontario Multidetector Computed Tomographic Coronary Angiography Study, or OMCAS, was conducted by PATH at McMaster University as a non-randomized diagnostic study to determine the sensitivity and specificity of multi-slice CTA compared to CA. Approximately 300 patients were recruited between September 2006 and June 2009 and final results from early 2010 are included in this report.

The radiation assessment was conducted by the University Health Network's (UHN) Usability Lab in Toronto with testing of 64-slice CT scanners under various conditions and indications to determine how best to balance image quality and radiation dose. The findings of this review are included in the section on safety. (7)

In 2008, the Health Technology Assessment Programme of the National Institute for Health Research in the UK published an HTA in the form of a systematic review of 64-slice or higher CT machines in the investigation of CAD. (6) Studies published in 2005 and 2006 for both suspected and existing CAD were reviewed, although for the purposes of the present analysis, our interest is in the diagnosis of CAD in patients suspected of having CAD. This subgroup of studies (n=18) were based on patient populations deemed to be at the higher end of pre-test risk. For example, some studies were assessing CAD in patients with previous valvular surgery or other types of interventions. As the present analysis is focused on intermediate risk CAD in native artery disease, studies from the UK HTA were not deemed appropriate for our review.

The most recent HTA was published by the Belgian Health Care Knowledge Centre (5) and includes studies published in 2007 and 2008. In total, four studies from this review were extracted and included in the present analysis. One of these four (8) reported on the accuracy of CTA in males and females separately, and has been included in this HTA as two separate studies, for a total of five derived from this HTA.

Belgian Health Care Knowledge Centre, 2008 (5)

Objective: To summarize the current evidence on 64-slice CTA as an imaging modality for the diagnosis of obstructive CAD in native coronary arteries. The focus was on single source 64-slice CTA compared to CA.

Search date: 2007 and part of 2008.

Studies included: Herzog 2007; Meijboom 2007(females only); Meijboom 2007 (males only); Shabestari 2007; Shapiro 2007.

Conclusions: The variability between trails was pronounced but for diagnosis of obstructive CAD in native coronary arteries, sensitivity was found to be 98.0% (95%CI: 96.6 - 99.0) and specificity was 82.3% (95%CI: 78.5-85.7).

This HTA examined the literature published in 2007 and part of 2008 for patients suspected of having CAD. Cited limitations of CTA were concerns over motion artefacts from rapid or irregular heart rhythm, artifacts from coronary artery calcium and substantial radiation dose. (5) Motion artifacts have been partly overcome by higher-slice CT machines enabling imaging during several heartbeats and by the administration of beta-blockers to decrease heart rates prior to the exam. Calcium build-up in arteries decreases visibility of all segments of the coronary arteries, thus, affecting the specificity of the test. Although reduction in radiation exposure levels is anticipated in the next few years (Expert consultation, December 2009), the present doses are considered an important risk to be considered.

The generalizability of results is also addressed in that patients in such diagnostic accuracy studies of CTA have been already scheduled for the more invasive CA and, therefore, considered at higher risk than most patients at low or intermediate pre-test risk for whom CTA is mainly indicated (Expert consultation, December 2009). Results of this HTA, with a focus on single source 64-slice machines (for heart rates of up to 65 beats per minute), gave rise to a sensitivity of 98.0% (95%CI: 96.6 - 99.0) yet a lowered specificity of 82.3% (95%CI: 78.5 - 85.7) for a per-patient analysis. These four studies (9-11) (12) were extracted from this HTA and included in the present analysis.

Medical Advisory Secretariat Review

Three non-randomized clinical trials assessing the accuracy of 64-slice CTA compared to CA in patients with suspected CAD were identified in the literature from 2008 and 2009. Studies included patients referred for the more invasive CA who were also tested with 64-slice CTA. These will be described below, followed by the five studies identified from the Belgian HTA. (5)

Table 2: Quality of Evidence of Included Studies (13)

Study Design	Level of Evidence†	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	0
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	3 + 5*
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modelling	4d	0
Case series presented at international conference	4(g)	0
	Total	8

RCT refers to randomized controlled trial;

* Five trials were extracted from the Belgian Health Care Knowledge Centre HTA, 2008 (6)

A diagnosis of CAD was defined as a stenosis of at least 50% of any coronary artery. The measures of accuracy systematically reported in these studies are sensitivity and specificity (see Table 3). Where the negative predictive and positive predictive values can be calculated, these are also reported. The negative predictive value (NPV), defined as the proportion of all negative tests that are true negatives, is calculated as:

$$\text{NPV} = \frac{\text{number true negatives}}{\text{number true negatives} + \text{number false negatives}}$$

The positive predictive value (PPV), defined as the proportion of all positive tests that are true positives, is similarly calculated as:

$$\text{PPV} = \frac{\text{number true positives}}{\text{number true positives} + \text{number false positives}}$$

Table 3: Summary of Characteristics of Studies Included in HTA

Author Location, sites	Patients	N, (Prevalence of CAD)	Sensitivity (95% CI)	Specificity (95% CI)
Miller et al., 2008 (14) Intl., 9 sites	Suspected or known CAD, 40+ yrs.	291, 56%	85% (79%-90%)	90% (83%-94%)
Budoff et al., 2008 (15) US, 16 sites	Intermediate risk, suspected CAD, 18+ yrs.	230, 24.8%	95% (85%-99%)	83% (76%-88%)
Meijboom et al., 2008 (16) Netherlands	Stable, unstable anginal chest pain, 50-70 yrs.	360, 68%	99% (98%-100%)	64% (55%-73%)
Meijboom et al., 2007 (10) Netherlands	Acute or stable chest pain	123 females, 51%	Females: 100% (93%-100%)	Females: 75% (62%-85%)
		279 males, 68%	Males: 99% (96%-100%)	Males: 90% (81%-95%)
Shabestari et al., 2007 (17) Iran	Suspected CAD	138, 76%	96% (91%-99%)	67% (47%-83%)
Shapiro et al., 2007 (12) US	Referred for CA	37, 78%	97% (80%-100%)	63% (20%-93%)
Herzog et al., 2007 (9) US	Atypical chest pain	55, 35%	100% (85%-100%)	83% (67%-94%)

The three most significant studies published on the accuracy of CTA compared to CA are the CORE-64 study (14), the ACCURACY trial (15), and a prospective, multicenter, multivendor study conducted in the Netherlands. (16)

The CORE-64 study was a multicenter trial conducted by Miller et al. on the use of 64-slice, 0.5 mm CTA compared to conventional CA among patients with suspected CAD. (14) A total of 291 patients with suspected or known disease and calcium scores of 600 or less who had been referred for CA were accrued across nine centers in the US, Europe, and South America. Patients were excluded if they had a history of cardiac surgery, an allergy to ionated contrast dye or dye-induced nephropathy, multiple myeloma, organ transplantation, elevated serum creatinine levels, atrial fibrillation, heart failure, aortic stenosis, percutaneous coronary intervention in past 6 months, intolerance to beta-blockers, or a body mass index (BMI) greater than 40. Investigators, physicians and patients were blinded to the results of CTAs, which was performed prior to CA. Eligible patients were 40 years of age or older, with a study CAD prevalence of 56%. The patient-level sensitivity was 85% (95%CI: 79 - 90), which is lower than that described in the remainder of the studies in Table 3, and the specificity was 90% (95%CI: 83% - 94%), the highest value reported among the studies. These comparative results may be partly explained by the strict selection of patients, which may have excluded subjects with increased calcification (increased calcification may give rise to decreased specificity), thus, giving rise to an increased specificity. As the two tests were both conducted in each patient, there is likely non-independence in the measures for true positives and true negatives, with increases in specificity giving rise to deceases in sensitivity. Further, the positive predictive value of 91% (95%CI: 86% - 95%) and the negative predictive value of 83% (95%CI: 75% - 89%) indicate that 64-slice CTA cannot replace conventional CA at the present time.

The ACCURACY trial (15), which included chest pain patients without known CAD but who had been referred for CA, reported a sensitivity of 95% (95%CI: 85% - 99%) and a specificity of 83% (95%CI: 76% - 88%) for a stenosis of greater than 50%. The PPV was 64% (95%CI: 53% - 75%) and the NPV was 99% (95%CI: 96% - 100%). The prevalence of CAD was lowest in this study (24.8%), which was likely attributable to the (younger) age limit used with patients as young as 18 years of age included.

With less severe disease in this study (as defined by the prevalence of CAD), one would expect decreased calcification giving rise to a greater specificity than observed by Miller et al. This, however, did not occur and a possible explanation is the inclusion of patients with an elevated coronary artery calcium score (mean ± SD Agatston score: 284 ± 538) and no exclusions based on BMI in this study. Budoff et al. conclude that no difference in accuracy was observed between obese and non-obese patients or for heart rates greater than or less than 65 beats per minute; however, Agatston calcium scores greater than 400 reduced specificity significantly.

Meijboom et al. (16) conducted a multicenter multivendor prospective non-randaomized study in the Netherlands. Patients (n=285) were between 50 and 70 years of age with acute and stable anginal chest pain referred for conventional CA. The prevalence of at least one stenosis of ≥50% lumen diameter reduction was 68%. In a patient-based analysis, the sensitivity of CTA compared to CA was high at 99% (95%CI: 98% - 100%), whereas the specificity was low at 64% (95%CI: 55% - 73%). Excluded from this study were patients with a previous history of percutaneous coronary stent placement, bypass surgery, impaired renal function, persistent arrhythmias, inability to hold a breath for 15 seconds, or a known allergy to ionated contrast agents. Approximately 25% of patients had a BMI greater than 30 and Agatston calcium scores ranged between 42 and 553, possible explanations for the reduced specificity in this study.

A previous publication by Meijboom et al. (10) compared the accuracy of 64-slice CTA with CA separately for men and women. Although gender stratification was not examined in this overall review of cardiac imaging, this data is included to provide some insight into potential differences in diagnostic accuracy between men and women. In a non-prospective study of 402 patients with acute or stable chest pain symptoms, women (N=123) had a lower disease prevalence (51%) than men (n=279) (51% vs. 68%, $p<0.010$). Women also had less severe disease, and lower Agaston calcium scores (146, range: 0 to 373) than men (207, range 18 to 530, $p<0.05$). On a patient-level analysis, the sensitivity and NPV was very good for both women and men (100% versus 99%, p=NS; 100% vs. 98%, p=NS). The specificity and PPV, however, was significantly lower in women (75% vs. 90%, $p <0.05$; 81% vs. 95%, $p<0.001$). The authors concluded that the equally high sensitivity in both genders reflects the ability to correctly rule out the presence of significant obstructive CAD with a negative scan reliably obviating the need for further downstream evaluation with invasive CA.

Two additional non-randomized studies by Shabestari et al. (11) and Shapiro et al. (12) reported a similar prevalence of CAD (defined as ≥50% stenosis) at approximately 77%. Measures of accuracy were also similar with Shabestari et al. (N=138) reporting a sensitivity of 96% (95%CI: 91-99), specificity of 67% (95%CI: 47% - 83%), PPV of 91% (95%CI: 84% - 96%), NPV of 83% (95%CI: 63% - 95%), and Shapiro et al. (N=38) reporting a sensitivity of 97% (95%CI: 80% - 100%), specificity of 63% (95%CI: 20% - 93%), PPV of 90%, and NPV of 83%. Neither study reported excluding patients with higher calcium scores or BMI.

Herzog et al. (9) conducted a prospective assessment of the accuracy of 64-slice CTA in 55 symptomatic chest pain patients referred for imaging with CA. Patient age ranged from 49 to 70 years of age and the prevalence of CAD (defined as ≥50% stenosis) was 35%. Similar to the Study of Budoff et al., the sensitivity was high at 100% and the specificity lower at 83%. Herzog et al. indicate that unlike other investigations, irregular heart beat, obesity and marked coronary calcification were not considered exclusion criteria. The inclusion of such patients was also permitted in the ACCURACY study by Budoff et al., in which the overall prevalence of CAD was approximately 25%.

To provide summary estimates of sensitivity, specificity, area under the SROC curve (AUC) and diagnostic odds rations (DORs), a meta-analysis of the eight above-mentioned studies was conducted. Pooled estimates of sensitivity and specificity were 97.7% (95%CI: 95.5% - 99.9%) and 78.8% (95%CI: 70.8% - 86.8%), respectively (see Table 4 and Figure 1). These results indicate that the sensitivity of

CTA is almost as good as CA, with the pooled estimate at almost 100%, whereas the specificity is poorer at approximately 79%. The DOR, was estimated at 156.95 (95%CI: 11.18 - 302.72); however, with further examination of this estimate, it was considered less robust than that of sensitivity and specificity and thus, given less weight in the overall interpretation of the evidence. The AUC was 0.9435 for this study but the inability to provide confidence estimates for this estimate also decreased it utility as an adequate outcome measure in this review.

A limitation of this meta-analysis is the significant heterogeneity between studies for both the pooled sensitivity and specificity (heterogeneity Chi-square p=0.000, Table 4). To minimize such statistical concerns, the analysis was restricted to studies of intermediate risk patients with no previous cardiac history such as myocardial infarct or atrial fibrillation. Nevertheless, the underlying prevalence of CAD ranged from 24.8% to 78% between studies, an indication that there still existed variability in the pre-test probabilities of disease among this intermediate risk stable population. Such variation in the prevalence of CAD, accompanied with differences in the proportion of calcification likely affects the specificity directly and the sensitivity indirectly across studies. The SROC curve, based on a bivariate model, is included below in Figure 2.

Table 4: Pooled Accuracy Estimates from Meta-Analysis of Eight Studies

	Pooled Sensitivity (95%CI)	Pooled Specificity (95%CI)
CTA vs. CA	0.977 (0.955-0.999)	0.788 (0.708-0.868)
Heterogeneity Chi-sq	P=0.000	P=0.000

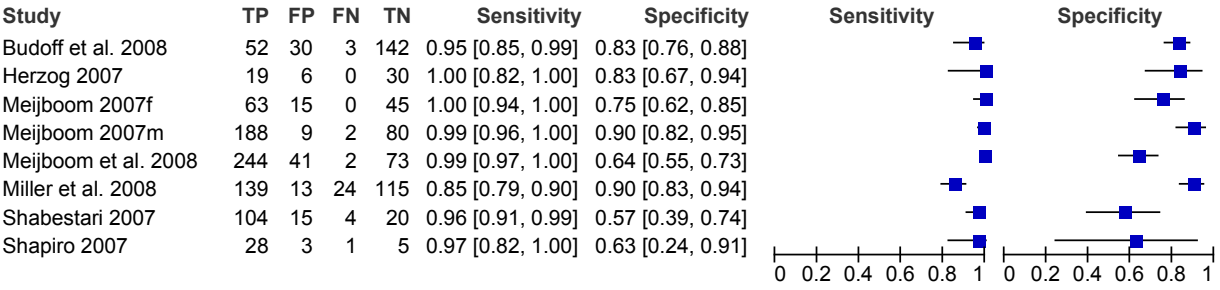

Figure 1: Forest Plot of Non-randomized Studies Assessing Sensitivity and Specificity of CTA vs. CA

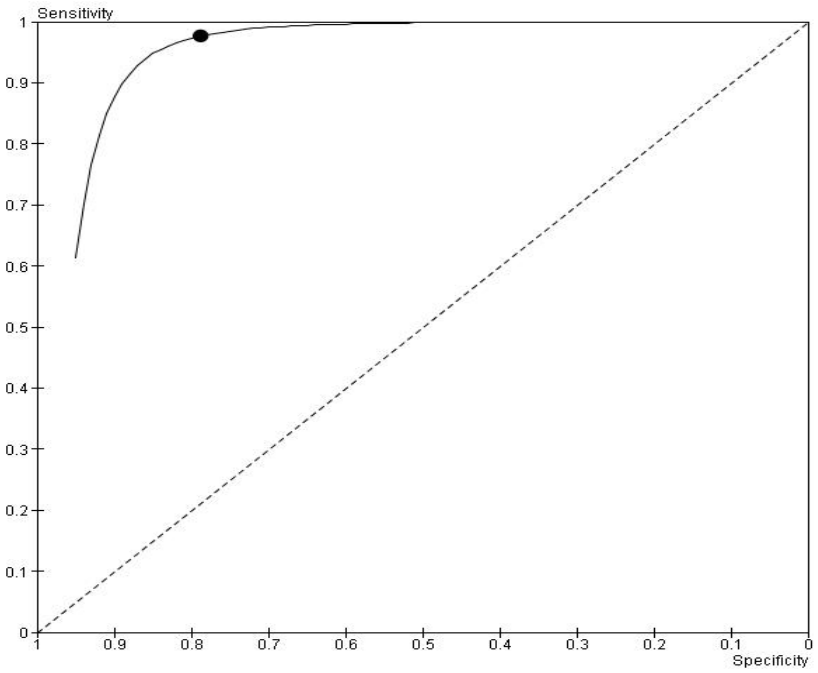

Figure 2: SROC Curve from Bivariate Model

In February 2010, results of the Ontario Multi-detector Computed Tomography Coronary Angiography Study (OMCAS) were available and included in a meta-analysis of the above studies. A non-randomized double-blind study conducted in three Ontarian centers, OMCAS was conducted as a result of a MAS review from 2005 requesting an evaluation of the accuracy of 64-slice CTA for detecting CAD as compared to CA. Within 10 days of their scheduled CA, all patients received an additional evaluation with CTA. Both tests were read by two blinded readers and any discrepancies resolved with a third consensus read. In total, 169 patients were enrolled in one of two groups within the study. Group 1 (n=52) included patients with valvular heart disease, congenital heart disease, or cardiomyopathy and who were, therefore, not included in this MAS review. Results from Group 2 (n=117) of the OMCAS trial comprised of patients with chest pain patients and at intermediate probability of CAD (10% - 90% probability) were included. The sensitivity and specificity results derived from these patients were 81.2% (95%CI: 71.9% - 89.6%) and 95.8% (95%CI: 85.7% - 99.5%), respectively.

Results of the meta-analysis with OMCAS included gave rise to a pooled sensitivity of 96.1% (95%CI: 94.0% - 98.3%) and a pooled specificity of 81.5% (95%CI: 73.0% - 89.9%), as displayed in Table 5 and Figure 3. Compared to the meta-analysis above, the addition of Ontario-specific data to this second meta-analysis did not have an effect on the sensitivity but gave rise to an increase in the pooled specificity (from 78.8% to 81.5%)

The diagnostic odds ratio, or DOR, was estimated at 108.60 (95%CI: 30.22 - 186.97), but as previously mentioned, this measure was given less weight in the overall interpretation of the evidence. The AUC was calculated to be 0.9622 (Figure 4). This improvement from 0.9435 is likely due to the increase in pooled specificity with the addition of the OMCAS study, but again, the inability to provide confidence estimates in this review decreases it utility as an adequate outcome measure.

Table 5: Pooled Accuracy Estimates from Meta-Analysis of Eight Studies and

	Pooled Sensitivity (95%CI)	Pooled Specificity (95%CI)
CTA vs. CA	0.961 (0.940-0.983)	0.815 (0.730-0.899)
Heterogeneity Chi-sq	P=0.000	P=0.000

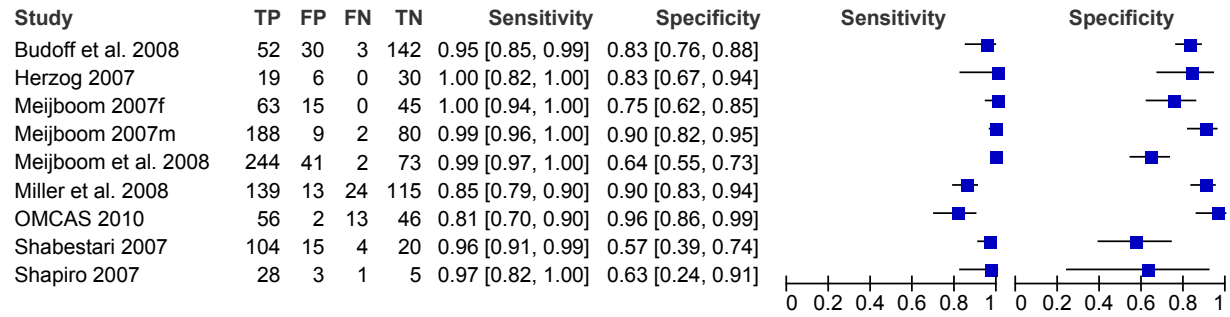

Figure 3: Forest Plot of Non-randomized Studies Assessing Sensitivity and Specificity of CTA vs. CA

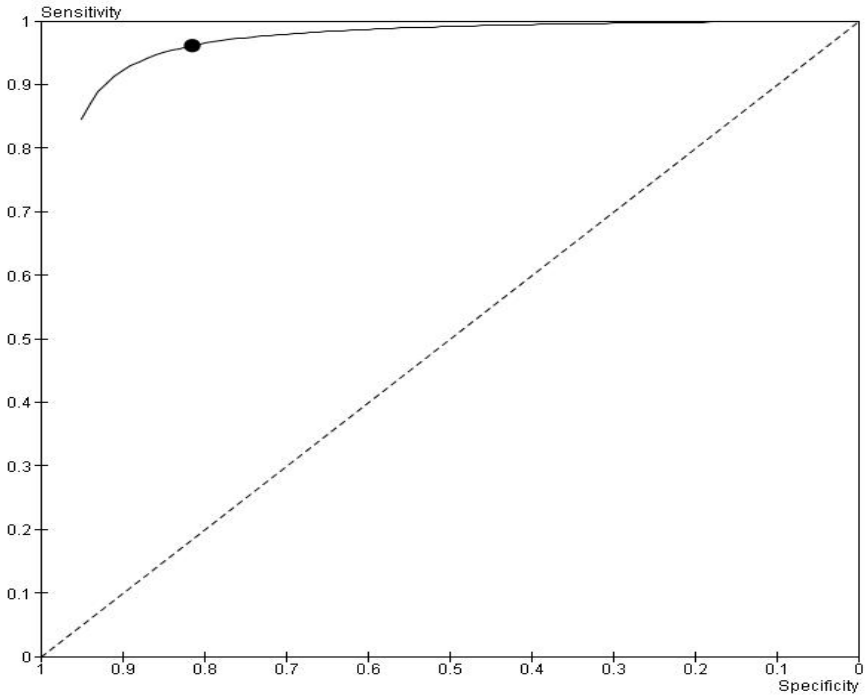

Figure 4: SROC Curve from Bivariate Model, OMCAS 2010 data included

Safety Concerns

The primary safety concern associated with CTA is the potential carcinogenicity from radiation exposure. The Healthcare Human Factors Group at the UHN published a 2006 review of such risks and possible approaches to reduce patient radiation exposure while retaining the benefits of this important diagnostic modality. (7) The appraisal consisted of a literature review, a survey of 20 Ontario healthcare institutions with 64-slice scanners, and interviews with CT experts. A summary of findings on (i) CT radiation dose and risks, and (ii) CTA, as cited in this 2006 report, are as follows:

CT Radiation Dose and Risks

In Canada, CT examinations grew by 8% between 2003/204 and 2004/2005. Currently, CT is estimated to account for approximately 10% of diagnostic examinations, yet over 60% of the total effective radiation dose from diagnostic imaging. The effective radiation dose from a typical CT examination of the chest is approximately equivalent to three times the amount of natural background radiation that each Canadian receives per year. The effective dose from CT, however, can be orders of magnitude greater than a traditional plain film examination (e.g., 400 times more radiation dose from a typical CT chest examination compared to plain film chest x-ray).

From 1991 to 1996 data, the cumulative risk of cancer to age 75 years attributable to diagnostic x-rays was estimated to be 1.1% in Canada, corresponding to 784 cases of cancer per year. These figures might be an underestimate because of the increasing radiation dose used for diagnostic x-rays in recent years. The cancer risk from 100 mSv (equivalent effective radiation dose of 10 typical abdominal CT examinations) was estimated by the National Research Council to be one out of 100 people, and six of 1000 people by the International Commission on Radiologic Protection. Lifetime radiation risks are particularly a concern for children because of their increased sensitivity and their longer expected lifespan following exposure compared to adults.

As a result of these findings, it has been recommended that CT examinations in Ontario be more closely monitored and standards developed. In particular, it is recommended that a provincial CT safety steering committee be established to be responsible for development of CT standards and monitoring of patient and staff CT radiation exposure, CT protocols and other methods of dose reduction, and the testing and inspection of CT scanners.

CTA

CTA has been suggested as a replacement for conventional diagnostic fluoroscopic CA. The dose estimates from coronary CTA have been found to range from 7 to 13 mSv, while dose estimates from conventional diagnostic CA have been found to range from 3 to 25 mSv. Therefore, the patient radiation dose from CTA appears to be within the same range as that from CA. The use of appropriate CTA protocol and techniques has been found to substantially reduce patient radiation dose. It is recommended that guidelines on CTA protocol parameters and techniques (e.g., prospective ECG gating) be established to minimize radiation exposure.

Summary of Findings

1. CTA is almost as good as CA in detecting true positives but poorer in the rate of false positives. The main value of CTA may be in ruling out significant CAD.
2. Increased prevalence of CAD decreases study specificity, whereas its specificity is increased in the presence of increased arterial calcification even in lower prevalence studies.
3. Positive CT angiograms may require additional tests such as stress tests or the more invasive CA, partly to identify false positives.
4. Radiation exposure is an important safety concern that needs to be considered, particularly for patients exposed to repeat CTAs.

Quality of Evidence

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (18) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High Further research is very unlikely to change confidence in the estimate of effect.

Moderate Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very Low Any estimate of effect is very uncertain

Table 6: GRADE Quality of Evidence for the Accuracy of CTA in the Diagnosis of Intermediate Risk CAD

Outcome	Explanation	GRADE
Design	8 non-randomize clinical trials	Moderate
Quality	All subjects exposed to both CTA and CA; heterogeneity in both summary estimates of sensitivity and specificity	Moderate → Low
Consistency	Consistent for sensitivity, more variation with specificity	Unchanged
Directness	The evidence is a direct evaluation of CT and CTA in CAD.	Unchanged
	Quality of evidence	**Moderate to Low**

Table 7: Factors Affecting GRADE Quality of Evidence

Factor	Explanation	Effect on GRADE
Risk of Bias		
Study design	▪ 8 non-randomized clinical trials	Moderate
Limitations	▪ Heterogeneity between studies for summary estimates.	Moderate → Low
Indirectness		
Outcomes	▪ Diagnostic tests are considered as intermediary steps in the clinical utility process. Clinical outcomes other than diagnosis of intermediate risk CAD were not examined.	Unchanged
Patient populations, diagnostic test, comparison test, and indirect comparisons	▪ Study population was intermediate risk CAD. CTA has been reported to be useful in symptomatic patients at low pre-test probability of CAD in addition to intermediate risk. Low pre-test risk patients were not included in the overall review of cardiac imaging.	Unchanged
Important inconsistency in study results	▪ No inconsistency	Unchanged
Imprecise evidence	▪ Confidence intervals for sensitivity, specificity were sufficiently precise.	Unchanged
Publication bias	▪ No publication bias	Unchanged
	Quality of evidence	**Low**

Existing Guidelines for CTA

Three guidelines documents addressing the diagnosis of CAD were identified. Although other patient populations such as asymptomatic patients and those with low pre-test risk of CAD were also included in these reports, these patient subgroups were not included in this MAS EBA.

CIGNA Medical Coverage Policy, effective December 15, 2009. (19)

CIGNA covers 64-slice or greater multidetector-row CTA as a medically necessary adjunct to other testing for ANY of the following indications:

- The evaluation of chest pain in an individual with a very low, low, or intermediate pre-test probability of CAD when the individual cannot perform or has a contraindication to exercise and chemical stress testing (i.e. exercise treadmill stress test, stress echo, and nuclear stress test)
- The exclusion of CAD in an individual with a low or very low pre-test probability of CAD when recent stress test results (i.e., exercise treadmill, stress echo, or nuclear stress test) are uninterpretable, equivocal, or there is a suspicion that the results are falsely positive
- The exclusion of CAD in an individual with an intermediate pre-test probability of CAD when recent stress test results (i.e., exercise treadmill, stress echo, or nuclear stress test) are uninterpretable or equivocal, AND CTA will be performed in lieu of an angiography.
- The exclusion of CAD in a symptomatic individual (e.g., acute chest pain in an emergency department setting) and the individual has an intermediate pre-angiography probability of CAD and there are no changes noted on the ECG and serial enzymes are negative
- The evaluation of suspected or known coronary artery anomalies associated with congenital conditions
- For morphologic evaluation of the coronary arteries in an individual with dilated cardiomyopathy or new onset heart failure, when ischemia is the suspected etiology and cardiac catheterization and/or nuclear stress test have not been performed
- Pre-operative assessment of coronary arteries in an individual undergoing repair of aortic dissection, aortic aneurysm repair or valvular surgery AND CTA will be performed in lieu of an angiography
- Post-coronary artery bypass grafting (CABG) when BOTH of the following criteria are met:
    - repeat intervention is being considered
    - recent coronary angiography has been completed but additional information is needed before a treatment decision can be made

AETNA Clinical Policy Bulletin: Cardiac CT, Coronary CT Angiography and Calcium Scoring, effective 04/09/1998; last review 05/06/2009, next review 03/11/2010. (20)

Aetna considers cardiac CTA of the coronary arteries using 64 slices or greater medically necessary for the following indications:

1. To rule out significant coronary stenosis in persons with a low or very low pre-test probability of CAD by Framingham risk scoring or by American College of Cardiology criteria with any of the following indications:
    a) Persons with chest pain who cannot perform or have contraindications to exercise and pharmacologic stress testing (see appendix); *or*
    b) Persons with a positive (i.e., greater than or equal to 1 mm ST segment depression) exercise stress test; *or*
    c) Persons with chest pain presenting to the emergency department when an imaging stress test or CA are being deferred as the initial imaging study.
2. The evaluation of asymptomatic persons at low pretest probability of coronary heart disease by Framingham risk scoring (see appendix) who have an equivocal exercise or pharmacological stress test. Note: Current guidelines from the American Heart Association recommend against routine stress testing for screening asymptomatic adults.
3. Preoperative assessment of persons scheduled to undergo 'high-risk" non-cardiac surgery, where an imaging stress test or invasive CA is being deferred unless absolutely necessary. The American College of Cardiology defines high-risk surgery as emergent operations, especially in the elderly, aortic and other major vascular surgeries, peripheral vascular surgeries, and anticipated prolonged surgical procedures with large fluid shifts and/or blood loss involving the abdomen and thorax.
4. Preoperative assessment for planned non-coronary cardiac surgeries including valvular heart disease, congenital heart disease, and pericardial disease, in lieu of cardiac catheterization as the initial imaging study.
5. The detection and delineation of suspected coronary anomalies in young persons (less than 30 years of age) with suggestive symptoms including: angina, syncope, arrhythmia, and exertional dyspnea (without other known etiology of these symptoms in children and adults) dyspnea, tachypnea, wheezing, periods of pallor, irritability (episodic crying), diaphoresis, poor feeding and failure to thrive in infants.

Harvard Pilgrim Health Care, effective 10/ 2006, revised 04/2009. (21)

CTA is covered in the evaluation of CAD.

Economic Analysis

DISCLAIMER: The Medical Advisory Secretariat uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

Downstream costs: All numbers reported are based on assumptions on population trends (i.e. incidence, prevalence and mortality rates), time horizon, resource utilization, patient compliance, healthcare patterns, market trends (i.e. rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents ***an estimate only***, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

Study Question

The objective of this economic analysis is to determine the cost effectiveness of CT angiography for the diagnosis of patients with suspected CAD, when compared to the following cardiac imaging modalities: stress echocardiography (ECHO), stress contrast echocardiography (contrast ECHO), single photon emission computed tomography (SPECT), and cardiac MRI. The relative cost-effectiveness of these five non-invasive cardiac imaging technologies was assessed in two patient populations: a) out-patients presenting with stable chest pain; and b) in-patients presenting with acute, unstable chest pain. Note that the term "contrast ECHO" used in the following sections refers to stress echocardiography performed with the availability of contrast medium if needed, due to poor image quality.

Economic Analysis Overview

For the two patient populations, decision-analytic cost-effectiveness analyses were conducted to evaluate the relative cost-effectiveness of the five non-invasive cardiac imaging technologies. Decision analytic models were developed for these patient populations with two reported outcomes: the cost per accurate diagnosis of CAD and the cost per true positive diagnosis of CAD. The physician and hospital costs for the tests were taken from 2009 Ontario Health Insurance Plan (OHIP) and the Ontario Case Costing Initiative (OCCI) administrative databases.(22;23) A budget impact analysis (BIA) was then performed to assess the effect of replacing a certain proportion of stress ECHO tests with other cost-effective, non-invasive modalities. The costs presented in this BIA were estimated from Ontario data sources from 2009; the volumes of tests performed were estimated from data from fiscal years 2002 to 2008.

Economic Literature Review

The purpose of the systematic review of economic literature was to identify, retrieve, and summarize studies evaluating the cost-effectiveness of selected cardiac imaging tests for the diagnosis of CAD. Medline and the National Health Service Economic Evaluation Database (NHSEED) were searched from

their inception up to October 2009. Included studies were those full economic evaluations describing both costs and consequences of CT angiography, Cardiac MRI, SPECT, and stress ECHO (with and without contrast) in the diagnosis of CAD. Article selection was performed by independent pairs of researchers. Target data for extraction included: study first author and year of publication, imaging tests compared, type of economic analysis, reported costs and outcomes, incremental cost-effectiveness ratio (ICER), currency, and patient characteristics (i.e. known or suspected CAD and risk of CAD). The primary outcome of interest was the ICER of each imaging test in relation to another test of interest.

Literature Search Results

A total of 883 non-duplicate citations were found from the two electronic databases after applying the literature search strategy. Based on the content of their abstracts, 147 full-text articles were retrieved for further assessment of their inclusion/exclusion. Of these, 122 were rejected, leaving 25 for inclusion. Following the data extraction process, 13 studies were excluded (24-35), with 12 studies being ultimately selected for analysis.(36-47)

Characteristics of included studies

From the 12 studies included, eight assessed the cost-effectiveness of two of the selected imaging tests (39-42;44;46;47), three studies evaluated three concomitant technologies (36;43;45), and one study evaluated five technologies.(37)

Five studies were cost-effectiveness analyses, where the most common outcome was cost per correct/successful CAD diagnosis.(36;37;44;46;47) The other seven were cost-utility analyses using cost per quality adjusted life years (QALYs) as their primary outcome.(38-43;45) The time-horizon used across the included studies ranged from 30 days to lifetime, with five studies having 25 years or more of follow-up.(38-40;42;46) The remaining studies used 18 months (45), 3 months (47), and 30 days of analytical time horizon.(41) Four studies did not report the time-horizon used in their analysis.(36;37;43;44)

All included studies evaluated at least one form of ECHO against one of the other remaining selected imaging tests.(36-47) The cost-effectiveness of SPECT was studied in nine studies.(36;38-40;42;43;45-47), three studies assessed CT angiography in comparison to stress ECHO or MRI.(37;41;44), while cardiac MRI was compared to each of the three other selected imaging tests in two studies.(37;45) No full economic analysis between CT angiography and SPECT was found in the published literature.

Literature results for CT angiography

CT angiography was compared to MRI and stress ECHO in three published economic evaluations (see Table 8).(37;41;44) Only one study reported an ICER value in which CT angiography was found to dominate (i.e., lower cost, better outcome) stress ECHO.(41) In the remaining studies, ICERs were not used, although the study authors stated that CT angiography was considered cost-effective in comparison to stress ECHO (37;44) and MRI (37) when the pre-test likelihood or prevalence of CAD was greater than or equal to 60%.

Table 8: Summary incremental cost-effectiveness ratios across selected studies evaluating CT angiography

Study	Comparator	Outcome of interest	Reported as cost-effective?	ICER
Dewey et al., 2007	MRI	Cost per QALY	Yes	Not reported*
Dewey et al., 2008	Stress ECHO	Cost per QALY	Yes	Not reported†
Khare et al., 1999	Stress ECHO	Cost per QALY	Yes	Dominant
Rumberger et al., 2004	Stress ECHO	Cost per correct diagnosis	Yes	Not reported‡

Abbreviations: CT Angio = CT Angiography

* At a pre-test likelihood of 60%, CT angiography was cost-effective.

† At a pre-test likelihood of 60%, CT angiography was cost-effective.

‡ For prevalence of disease <=70%, CT angiography was considered cost-effective.

Conclusion of systematic review

Overall, CT angiography was found to be cost-effective or cost-saving in all four of the comparisons of that technology; stress ECHO was found cost-effective in eight of the 13 comparisons in which it was evaluated; and SPECT was found cost-effective in three of nine comparisons. Cardiac MRI was not found to be cost-effective or cost-saving in any of the four comparisons found.

According to the published economic data, CT angiography is often found to be cost-effective when compared to other technologies. SPECT and stress ECHO were also found to be cost-effective in several of the comparative studies examined, while cardiac MRI was not cost-effective in any study. Limitations to these conclusions apply, such as the analyses found in the literature evaluated other forms of the selected cardiac imaging tests which might change the proposed relative cost-effectiveness.

Decision analytic Cost Effectiveness Analysis

Design

This study was designed as a cost effectiveness analysis, with primary results reported as incremental cost per true positive diagnosis, or incremental cost per accurate diagnosis.

Target Population and Perspective

Two populations were defined for evaluating the cost-effectiveness of an accurate diagnosis (i.e. true positive and true negative diagnoses) of CAD: a) out-patients presenting with stable chest pain; and b) in-patients presenting with acute, unstable chest pain. The first population was defined as persons presenting with stable chest pain, with an intermediate risk of CAD following physical examination and a graded exercise test, as defined by the American College of Cardiology / American Heart Association 2002 Guideline Update for the Management of Patients with Chronic Stable Angina.(48) The second population was defined as persons presenting to emergency for acute, unstable chest pain, and who are admitted to hospital, as defined by the American College of Cardiology / American Heart Association 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction.(49) The analytic perspective was that of the Ontario Ministry of Health and Long-Term Care (MOHLTC).

Comparators and Parameter Estimates

The imaging technologies that were compared in the current cost-effectiveness analysis included: CT angiography, stress ECHO (with and without contrast), cardiac perfusion stress MRI, and attenuation-

corrected SPECT. Test characteristic estimates (i.e., specificity, sensitivity, accuracy) for each imaging technology were obtained from the systematic review and meta-analysis conducted by MAS and the MOHLTC. Table 9 shows a list of the parameters with corresponding 95% confidence intervals used for both the outpatient and inpatient decision-analytic cost-effectiveness models.

The average wait-time for each cardiac imaging test was measured as the additional days needed to wait for a non-invasive test compared to the average wait time for a typical graded exercise stress test (GXT). The proportion of tests deemed uninterpretable by expert opinion is shown, with a corresponding range of high and low values. The probability of receiving pharmacological stress versus exercise stress is not listed, but reported here for completeness: approximate values of 30% for the stable, outpatient population and 80% for the unstable, inpatients.

Table 9: Parameter estimates for CT angiography tests: sensitivity, specificity; additional days needed to wait for specific cardiac tests; proportion of non-invasive tests considered uninterpretable

Pooled Diagnostic Accuracy	Point Estimate	95% Lower	95% Upper
CAD diagnosis: Sensitivity	0.972	0.954	0.990
CAD diagnosis: Specificity	0.787	0.688	0.886
Additional time for test (compared to GXT)	**Average**	**Low**	**High**
Inpatient population: Additional days for test	3.0	0.5	7.0
Uninterpretable test result	**Average**	**Low**	**High**
Outpatient population: % of tests that are uninterpretable	5.3%	3.0%	8.0%
Inpatient population: % of tests that are uninterpretable	7.5%	5.0%	10.0%

Note: Sensitivity and specificity estimates are taken from the effectiveness literature review of CT angiography. Other estimates are based on consultations with experts in cardiology.

Time Horizon and Discounting

The time horizon for both decision-analytic models (i.e., for outpatient and inpatient populations) was the time required to determine an accurate, or true positive diagnosis of CAD. As a result, the actual time taken to determine the CAD status of patients may differ across non-invasive test strategies.

Model Structure and Outcomes

Figure 5 provides a simplified illustration of the decision-analytic model structure used for the outpatient and inpatient populations. The following two simplifying assumptions were made for the models:

1. When results of the first cardiac imaging test are un-interpretable, a patient will undergo a second cardiac test. This test will be one of the four remaining tests that were not used as the first test
2. Should a second test be required, the type of stress (pharmacological or exercise) that a patient receives will be the same type of stress as used in the first.

The short-term outcome presented in this report focuses on an accurate diagnosis of CAD (i.e., true positive and true negative test results). A second outcome of true positive diagnosis was examined for the two models, with results reported in The Relative Cost-effectiveness of Five Non-invasive Cardiac Imaging Technologies for Diagnosing Coronary Artery Disease in Ontario. (50)

Sensitivity Analyses

Various sensitivity analyses were conducted for the outpatient and inpatient populations. First, the prevalence of CAD was varied from 5% to 95% in 5% increments, while all other model estimates were held constant. Willingness-to-pay (WTP) was also varied and a range of results were presented. Second, one-way sensitivity analyses were conducted in which selected estimates were varied over plausible ranges. The varied parameters included sensitivity and specificity estimates, wait times for imaging tests performed in hospital, as well as the costs of CT angiography, ECHO tests, and cardiac MRI. A third series of sensitivity analyses was conducted that specifically addressed the possibility of unavailable imaging technologies.

Additional details of the sensitivity analyses performed can be found in The Relative Cost-effectiveness of Five Non-invasive Cardiac Imaging Technologies for Diagnosing Coronary Artery Disease in Ontario. (50) The results of the sensitivity analyses are summarized in the Results and Discussion section below.

Resource Use and Costs

Resource use and costs were derived from Ontario data sources: the OHIP and OCCI administrative databases.(22;23) The cost of conducting each cardiac test was calculated as the sum of the test's respective professional fees and technical fees, as described in the Ontario Schedule of Benefits, as listed in Table 10. Please refer to the The Relative Cost-effectiveness of Five Non-invasive Cardiac Imaging Technologies for Diagnosing Coronary Artery Disease in Ontario (50) for a full description of resource allocation and costs for the non-invasive cardiac tests.

Note that for ECHO tests with available contrast agent, the cost for the contrast medium was added whenever the contrast was used in the event of uninterpretable ECHO test result. The cost of this contrast medium was estimated as $170 per vial (single use) through consultation with industry experts. Only this cost was added to the base test cost of contrast ECHO. In general, where an imaging test result was uninterpretable, an additional cost of follow-up with the patient (physician fee) was incurred, as well as the cost for conducting another cardiac imaging test. For out-patients presenting with stable chest pain, a consultation professional fee of $30.60 (OHIP code A608 for "partial assessment") was used after an uninterpretable test result (one time cost).

In the case of patients presenting with acute, unstable chest pain, costs for inpatient hospitalization were also included in the model. The total cost of hospitalization was calculated based on the average wait time for each cardiac imaging test and a cost per diem for each day spent in hospital (for the CT angiography wait time, see Table 9). An additional consultation fee was also used only for the inpatient population: $29.20 (OHIP code C602 for "subsequent visit- first five weeks") was used for each inpatient day spent in hospital.

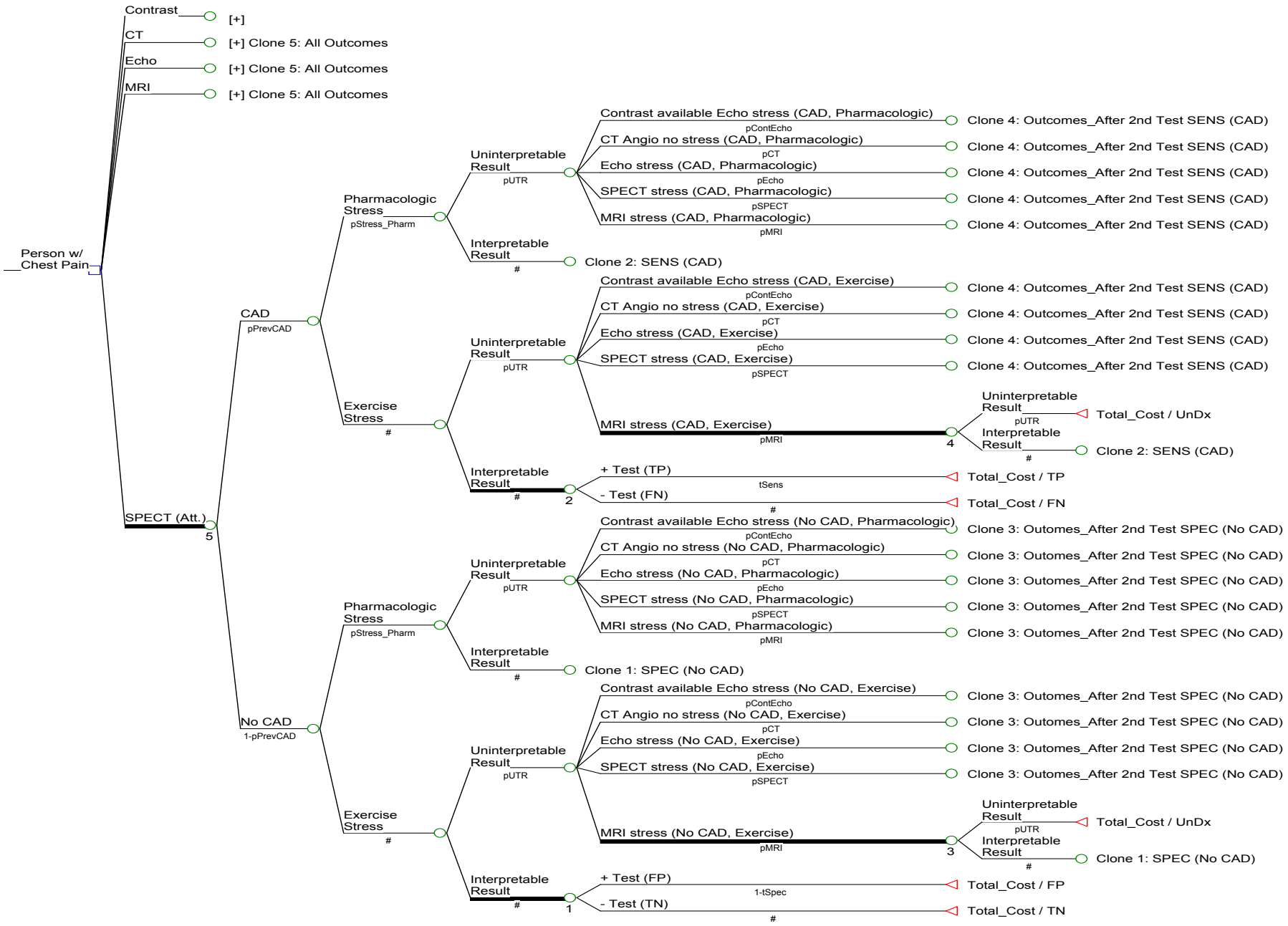

Figure 5: Decision analytic model used to evaluate the cost-effectiveness of cardiac imaging technologies for the diagnosis of CAD

Table 10: List of cardiac imaging tests and associated OHIP 2009 costs

Technology		List of professional fees				Subtotal	List of technical fees					Subtotal	Total
Cardiac CT	Fee code	X125	X417				Imputed						
	Cost	$89.20	$64.00			**$153.20**	$336.52					**$336.52**	**$489.72**
Cardiac MRI (dobutamine stress with gadolinium contrast)	Fee code	X441	X445	X487	G319		Imputed	G315	G174				
	Multiplier	1.0	3.0	1.0	1.0		1.0	1.0	1.0				
	Cost	$75.55	$37.80	$37.75	$62.65	**$289.35**	$463.06	$33.65	$37.00			**$533.71**	**$823.06**
Cardiac SPECT (exercise stress)	Fee code	J866	J811	J807	G319		J866	J811	J807	G315			
	Cost	$28.70	$55.30	$47.00	$62.65	**$193.65**	$44.60	$97.55	$223.15	$33.65		**$398.95**	**$592.60**
Cardiac SPECT (dobutamine stress)	Fee code	J866	J811	J807	G319		J866	J811	J807	G315	G174		
	Cost	$28.70	$55.30	$47.00	$62.65	**$193.65**	$44.60	$97.55	$223.15	$33.65	$37.00	**$435.95**	**$629.60**
Cardiac SPECT (dipyramidole stress)	Fee code	J866	J811	J807	G112		J866	J811	J807	G111			
	Cost	$28.70	$55.30	$47.00	$75.00	**$206.00**	$44.60	$97.55	$223.15	$41.10		**$406.40**	**$612.40**
ECHO (exercise stress)	Fee code	G571	G578	G575	G319		G570	G577	G574	G315			
	Cost	$74.10	$36.90	$17.45	$62.65	**$191.10**	$76.45	$45.15	$16.45	$33.65		**$171.70**	**$362.80**
ECHO (dobutamine stress)	Fee code	G571	G578	G575	G319		G570	G577	G574	G315	G174		
	Cost	$74.10	$36.90	$17.45	$62.65	**$191.10**	$76.45	$45.15	$16.45	$33.65	$37.00	**$208.70**	**$399.80**
ECHO (dipyramidole stress)	Fee code	G571	G578	G575	G112		G570	G577	G574	G111			
	Cost	$74.10	$36.90	$17.45	$75.00	**$203.45**	$76.45	$45.15	$16.45	$41.10		**$179.15**	**$382.60**

Notes: Fee codes are taken from the 2009 OHIP fee schedule.(23) Imputed technical fees were based on the proportion of average technical fees associated with above ECHO and SPECT fee code combinations. For cardiac SPECT and ECHO stress tests, an average test cost was calculated using dobutamine and dipyramidole fee codes.

Willingness-to-pay

The WTP must be determined by the MOHLTC. As such, all reasonable WTP values are presented in the Results and Discussion section and interpreted at two WTP 'anchors' representing the estimated cost of the most expensive non-invasive test considered in our model (cardiac MRI perfusion, $804) and the estimated cost of a coronary angiography ($1,433). These anchors are only intended to guide discussion.

Note that the following points might be useful in determining the WTP:

- An "accurate diagnosis" of CAD can be obtained through a coronary angiography for $1,433. It would thus be reasonable to expect the WTP for an accurate diagnosis through a non-invasive test to resemble this amount; however, an accurate diagnosis does not include the value or benefit of providing additional diagnostic or prognostic information from either non-invasive imaging or coronary angiography
- The MOHLTC is currently willing to pay up to $804 for a non-invasive test with less-than-perfect diagnostic accuracy. Its willingness to pay for an accurate diagnosis from such a test thus appears to be greater than $804.
- While coronary angiography is invasive, the other tests are non-invasive and would presumably be of greater value (i.e., incur a higher premium). These tests do, however, impose risks not applicable to coronary angiography, such as increased radiation exposure and adverse reaction to contrast agents
- These tests are not perfectly accurate. An accurate diagnosis from such a test may be valued less than one from a coronary angiography

Results and Discussion

As shown in Tables 11 and 12, CT angiography was dominated by both CT angiography and contrast ECHO (that is, it had higher costs and was less effective) in both populations for the outcome of interest. CT angiography did, however, dominate stress ECHO, SPECT, and MRI, having lower costs and while being more effective. In stable outpatients, CT angiography had an ICER of $1,527 per accurate diagnosis compared to contrast ECHO (the strategy with the lowest costs). This value lies above both willingness-to-pay (WTP) anchors ($804 and $1,433 per accurate diagnosis respectively), suggesting that, at either of these anchors, contrast ECHO is more cost-effective than CT angiography. In the acute inpatient population, CT angiography dominated only MRI. The ICER of CT angiography versus attenuated SPECT was $18,981 per accurate diagnosis, suggesting that CT angiography is not cost-effective for such patients (although this result is driven by the relatively long hospital wait time assumed for CT angiography; this assumption was revisited in a scenario analysis described below).

The two-way sensitivity analysis of WTP and prevalence of CAD revealed that, at the two WTP anchors of $804 and $1,433 per accurate diagnosis, CT angiography was considered cost-effective in the stable outpatient population when the prevalence of CAD was greater than 70% or 50% respectively. In addition, when contrast ECHO was removed from the analysis, CT angiography was the most cost-effective strategy irrespective of the prevalence or anchor used. Few changes were observed when varying other model parameters such as the percentage of uninterpretable stress ECHOs. For acute inpatients, the data used for hospital wait times in the base case analysis was derived from expert opinion and the number of wait days for CT angiography was greater than all other strategies. Where the number of hospital waiting days for each test was instead normalized at 1.5 days across all strategies, CT angiography appeared cost-effective only at the higher WTP anchor and where the prevalence of CAD was greater than 80%.

An additional sensitivity analysis was performed using the estimates of diagnostic sensitivity and specificity of CT angiography reported by the Ontario Multidetector Computed Tomographic Coronary

Angiography Study (OMCAS).(51) Through correspondence with Programs for Assessment of Technology in Health (PATH), the following estimates of sensitivity and specificity were taken from the study's 'group 2' patients (intermediate probability of CAD, 50% stenosis): 0.812 and 0.958, respectively. When combined with the estimates from the current effectiveness review and meta-analysis (0.972 sensitivity, 0.787 specificity), the resulting estimates of 0.961 sensitivity and 0.815 specificity were used in the sensitivity analysis. These new estimates of diagnostic accuracy for CT angiography did not alter the results of the cost-effectiveness analysis.

To summarize, CT angiography appears to be a cost-effective diagnostic strategy in outpatients with stable chest pain only at higher prevalence rates of CAD. In acute inpatients, CT angiography was not considered cost-effective in the base-case analysis; however, the estimates used in the base case analysis for the number of wait days in hospital for a diagnostic test were based on expert opinion alone and disadvantages CT angiography. When the number of wait days in hospital across all tests was normalized, CT angiography appears to be cost-effective only at the higher WTP anchor and for a very high prevalence of CAD.

Table 11: Cost-effectiveness analysis base case results for stable outpatients

Technology	Cost (C)	Δ Cost	Effect (E)	Δ Effect	C / E	ICER
Stress contrast ECHO	$433.49		81.8%		$530	N/A
CT angiography	$517.73	$84.24	87.4%	5.52%	$593	$1,527
Stress ECHO	$551.58		81.1%		$680	(Dominated)
SPECT	$634.63		82.8%		$766	(Dominated)
Cardiac MRI	$835.47		85.2%		$981	(Dominated)

Table 12: Cost-effectiveness analysis base case results for acute inpatients

Technology	Cost (C)	Δ Cost	Effect (E)	Δ Effect	C / E	ICER
Stress contrast ECHO	$1,794.58		81.9%		$2,190	N/A
SPECT	$1,982.91	$188.32	83.9%	1.99%	$2,363	$9,489
Stress ECHO	$2,550.87		81.5%		$3,129	(Dominated)
CT angiography	$3,267.39	$1,284.48	87.5%	3.56%	$3,735	$36,055
Cardiac MRI	$4,918.02		85.6%		$5,749	(Dominated)

Budget Impact Analysis

The budget impact analysis (BIA) was performed taking the perspective of the MOHLTC and includes both physician and hospital (clinic) costs of non-invasive cardiac imaging tests. Volumes of cardiac tests in Ontario were taken from administrative databases (OHIP, DAD, NACRS) for fiscal years 2004 to 2008 using methodology summarized in The Relative Cost-effectiveness of Five Non-invasive Cardiac Imaging Technologies for Diagnosing Coronary Artery Disease in Ontario. (50) The following technologies were considered in the current BIA for the diagnosis of CAD: ECHO (including both stress and stress with contrast agent available), nuclear cardiac imaging (including MPI and SPECT tests), cardiac MRI, and CT angiography.

In the current BIA, the effect of moving a certain proportion of the volume of specific tests to another, substitute technology was assessed for various scenarios. These scenarios are presented irrespective of whether a technology was found to be cost-effective and are reported as general reference tables. To summarize briefly, CT angiography lies in the mid-range of test costs of the compared cardiac imaging modalities. When the volume of CT angiography tests is shifted to other technologies, some scenarios result in higher projected costs, while others result in lower project costs. If 25% of the CT angiography tests is moved to other imaging technologies, ensuing projected costs would be as follows: the largest cost avoidance would be $53.8K per year for stress ECHO imaging, and the largest cost difference would be $156.7K per year for cardiac MRI (with cardiac MRI being the more expensive option). The largest possible cost avoidance corresponds to replacing 50% of CT angiography tests with stress ECHO ($107.6K per year); the largest possible cost difference corresponds to replacing 50% of CT angiography tests with cardiac MRI ($313.4K per year). Note that “cost avoidance” and “cost difference” are used here to represent “cost savings” and “increased cost”, respectively.

Appendix: Literature Search Strategies

Search date: July 20, 2009
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to November Week 2 2009>
Search Strategy

1 exp Myocardial Ischemia/ (307680)
2 (coronary adj2 arter* disease*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (60000)
3 ((myocardi* or heart or cardiac or coronary) adj2 (viable or viability or perfusion or function or isch?emi* or atheroscleros* or arterioscleros* or infarct* or occlu* or stenos* or thrombosis)).mp. (264645)
4 (myocardi* adj2 (stun or hibernat*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (852)
5 (stenocardia* or angina).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (54371)
6 heart attack*.mp. (2960)
7 exp Heart Failure/ (68049)
8 ((myocardi* or heart or cardiac) adj2 (failure or decompensation or insufficiency)).mp. (110792)
9 exp Ventricular Dysfunction, Left/ (15499)
10 (left adj2 ventric* adj2 (dysfunction* or failure or insufficienc*)).mp. (23480)
11 or/1-10 (473406)
12 exp Tomography, X-Ray Computed/ (226587)
13 ((coronary or heart or cardiac or myocardi* or angiograph*) adj2 ((computed adj2 tomograph*) or CT or multislice or multi-slice or multi-detector or multidetector or spiral or helical or MDCT or CAT)).ti,ab. (10282)
14 12 or 13 (229456)
15 11 and 14 (7457)
16 limit 15 to (controlled clinical trial or meta analysis or randomized controlled trial) (182)
17 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ (44264)
18 (health technology adj2 assess$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (885)
19 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (90196)
20 exp Random Allocation/ or random$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (623476)
21 exp Double-Blind Method/ (107385)
22 exp Control Groups/ (1301)
23 exp Placebos/ (29442)
24 (RCT or placebo? or sham?).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (184334)
25 or/16-24 (811661)
26 15 and 25 (395)
27 limit 26 to (english language and humans and yr="2004 -Current") (241)

Database: EMBASE <1980 to 2009 Week 47>
Search Strategy

1 exp ischemic heart disease/ (242917)
2 exp coronary artery disease/ (90631)
3 exp stunned heart muscle/ (1542)
4 (coronary adj2 arter* disease*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (72997)
5 ((myocardi* or heart or cardiac or coronary) adj2 (viable or viability or perfusion or function or ischemi* or atheroscleros* or arterioscleros* or infarct* or occlu* or stenos* or thrombosis)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (280716)

6 (myocardi* adj2 (stun or hibernat*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1066)
7 (stenocardia* or angina).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (46940)
8 heart attack*.mp. (2073)
9 exp heart failure/ (128424)
10 ((myocardi* or heart or cardiac) adj2 (failure or decompensation or insufficiency)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (110098)
11 exp heart left ventricle failure/ (9572)
12 (left adj2 ventric* adj2 (dysfunction* or failure or insufficienc*)).mp. (16434)
13 or/1-12 (438523)
14 exp computed tomographic angiography/ (6679)
15 ((coronary or heart or cardiac or myocardi* or angiograph*) adj2 ((computed adj2 tomograph*) or CT or multislice or multi-slice or multi-detector or multidetector or spiral or helical or MDCT or CAT)).ti,ab. (9805)
16 15 or 14 (13373)
17 16 and 13 (3272)
18 limit 17 to (human and english language and yr="2004 -Current") (2323)
19 Randomized Controlled Trial/ (176320)
20 exp Randomization/ (27165)
21 exp RANDOM SAMPLE/ (1679)
22 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (315687)
23 (health technology adj2 assess$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (745)
24 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (71929)
25 Double Blind Procedure/ (74829)
26 exp Triple Blind Procedure/ (14)
27 exp Control Group/ (5005)
28 exp PLACEBO/ or placebo$.mp. or sham$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (227731)
29 (random$ or RCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (458380)
30 (control$ adj2 clinical trial$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (298678)
31 or/19-30 (845455)
32 18 and 31 (256)

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